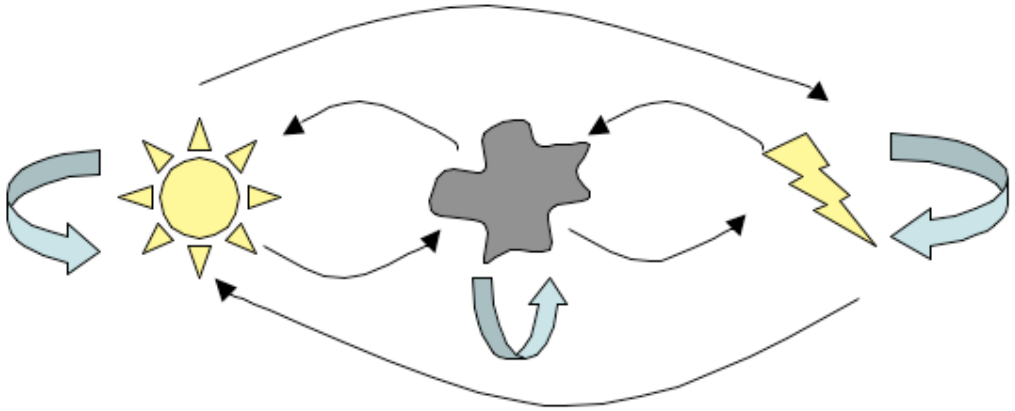
Baum-Welch and HMM applications

Analysis of Biological Sequences 140.638

Markov chains

- 3 states of weather: sunny, cloudy, rainy
  - Observed once a day at the same time



  - All transitions are possible, with some probability
  - Each state depends only on the previous state

Hidden Markov Models

Weather yesterday \ Weather today	Sunny	Cloudy	Rainy
Sunny	0.50	0.20	0.30
Cloudy	0.10	0.60	0.30
Rainy	0.20	0.40	0.40

All we observe is the dog:

IOOOIPIIIOOOOOPPIIIIIPI

	Dog: in	out	porch
Sun	0.2	0.7	0.1
Cloud	0.4	0.4	0.2
Rain	0.7	0.1	0.2

Hidden Markov Models: the three questions

Evaluation

Given: a HMM, M, and a sequence x
Find: P(x|M)
Forward, Backward and Forward-Backward algorithms

Decoding

Given: a HMM, M, and a sequence x
Find: the sequence Q of states that maximizes P(x,Q|M)
Viterbi algorithm

Learning

Given: an unknown HMM, M, and a sequence x
Find: parameters θ that maximize P(x|θ, M)
Baum-Welch expectation maximization (EM) algorithm

review

x are observations $\in A$, $q_1 \ldots q_n$ are hidden states $\in S$

$$\alpha(t,i) = p(x_1 x_2 \ldots x_t, q_t = S_i)$$

$$\beta(t,i) = p(x_T x_{T-1} \ldots x_t | q_t = S_i)$$

$$p(x, q_t = S_i | M) = \alpha(t,i)\beta(t,i)$$

$$p(x|M) = \sum_{i=1}^{N} \alpha(T,i) \qquad p(x|M) = \sum_{i=1}^{N} \beta(1,i)$$

Baum-Welch expectation maximization algorithm

You have: observed data

You want: parameters of the HMM that generated that data

Problem: the calculation space is too big for exact calculation -> use heuristic method (even though it's a partial solution it's very useful!)

We are finding locally optimal parameters.

Baum-Welch expectation maximization algorithm

Assume: data come from some random process that we can fit to a HMM

Assumption #1: alphabet A and the number of states, N, are fixed. Transition, emission and initial distribution probabilities are all unknown.

Baum-Welch expectation maximization algorithm

Assumption #2: data are a set of observed sequences $\{x^{(d)}\}$ each of which has a hidden state sequence Q^d

Assumption #3: we can set all parameters/probabilities to some initial values

- Can choose from some uniform distribution
- Can choose to incorporate some prior knowledge
- Can just be random
- Cannot be flat

Baum-Welch expectation maximization algorithm

$$\alpha(t,i) = p(x_1 x_2 \ldots x_t, q_t = S_i)$$

$$\beta(t,i) = p(x_T x_{T-1} \ldots x_t | q_t = S_i)$$

$$p(x, q_t = S_i | M) = \alpha(t,i)\beta(t,i)$$

$$P(q_t=S_i,\ q_{t+1}=S_\ell \mid x,\theta) = [\alpha(t,\ i)p_{i\ell}b_\ell(x_{t+1})\beta(t+1,\ell)]/P(x)$$

$$p'_{i\ell} = \sum_d 1/P(x^d) \sum_t \alpha^d(t,\ i)p_{i\ell}b_\ell(x^d_{t+1})\beta^d(t+1,\ell)$$

$$b'_\ell(c) = \sum_d 1/P(x^d) \sum_{t|x^d_t=c} \alpha^d(t,\ell)\beta^d(t,\ell)$$

Baum-Welch expectation maximization algorithm

$$P(q_t=S_i,\ q_{t+1}=S_\ell \mid x,\theta) = [\alpha(t, i)p_{i\ell}b_\ell(x_{t+1})\beta(t+1,\ell)]/P(x)$$

$$x_1 x_2 x_3 \cdots x_t x_{t+1} \cdots x_{T-1} x_T$$

$$q_1 q_2 q_3 \cdots q_t q_{t+1} \cdots q_{T-1} q_T$$

$$\cdots S_i S_l \cdots$$

Baum-Welch expectation maximization algorithm

$$P(q_t=S_i,\ q_{t+1}=S_\ell \mid x,\theta) = [\alpha(t,\ i)p_{i\ell}b_\ell(x_{t+1})\beta(t+1,\ell)]/P(x)$$

$$p'_{i\ell} = \sum_d 1/P(x^d) \sum_t \alpha^d(t,\ i)p_{i\ell}b_\ell(x^d_{t+1})\beta^d(t+1,\ell)$$

Figure out the probability of a hidden state i->ℓ transition

1) postulate that transition at every single spot in every single observed sequence (separately)
2) see how those probabilities compare to the best probabilities for those observed sequences
3) use that ratio for the updated $p_{i\ell}$ transition probability

Baum-Welch expectation maximization algorithm

$$P(q_t=S_i,\ q_{t+1}=S_\ell \mid x,\theta) = [\alpha(t,\ i)p_{i\ell}b_\ell(x_{t+1})\beta(t+1,\ell)]/P(x)$$

$$b'_\ell(c) = \sum_d 1/P(x^d) \sum_{t|x^d_t=c} \alpha^d(t,\ell)\beta^d(t,\ell)$$

Figure out the probability of an emission of symbol c from hidden state ℓ

1) postulate that hidden state under every symbol c in every single observed sequence (separately)
2) see how those probabilities compare to the best probabilities for those observed sequences
3) use that ratio for the updated $b'_\ell(c)$ transition probability

Baum-Welch expectation maximization algorithm

Then recalculate $P(x^d|M, \theta)$ for all observed data in the learning set (use Forward, Backward, or Forward/Backward to do this)

Rinse & repeat . . .

Successive iterations increase P(data) and we stop when the probability stops increasing significantly (usually measured as log-likelihood ratios).

Baum-Welch example

- I observe dog #2 at noon every day. Sometimes he's inside, sometimes he's outside.
- I guess that since he can't open the door by himself (yet) that there is another factor, hidden from me, that determines his behavior
- Since I am lazy I will guess that there are only two hidden states

Baum-Welch example

- guessing two hidden states. I need to invent a transition matrix and an emission matrix.

today

yesterday

	S1	S2
S1	0.5	0.5
S2	0.4	0.6

	in	out
S1	0.2	0.8
S2	0.9	0.1

initial: p(S1) = 0.3, p(S2) = 0.7

Baum-Welch example

one set of observations: `II, II, II, II, IO, OO, OI, II, II`

today

yesterday	S1	S2
S1	0.5	0.5
S2	0.4	0.6

	in	out
S1	0.2	0.8
S2	0.9	0.1

initial: p(S1) = 0.3, p(S2) = 0.7

Baum-Welch example

guess: if `II` came from S1•S2 the probability is

0.3 * 0.2 * 0.5 * 0.9 = 0.027

today

yesterday	S1	S2
S1	0.5	0.5
S2	0.4	0.6

	in	out
S1	0.2	0.8
S2	0.9	0.1

initial: p(S1) = 0.3, p(S2) = 0.7

Baum-Welch example

estimating the transition matrix:

Seq	P(Seq) if S1•S2	Best P(seq)
II	0.027	0.3403 S2•S2
II	0.027	0.3403 S2•S2
II	0.027	0.3403 S2•S2
II	0.027	0.3403 S2•S2
IO	0.003	0.2016 S2•S1
OO	0.012	0.096 S1•S1
OI	0.108	0.108 S1•S2
II	0.027	0.3403 S2•S2
II	0.027	0.3403 S2•S2
Total	0.285	2.4474

Our estimate for the S1->S2 transition probability is now 0.285/2.4474 = 0.116. Calculate the S2->S1, S2->S2, S1->S1 as well and normalize so they add up to 1 as needed, to update the transition matrix.

Baum-Welch example

estimating the emission matrix:

Seq	Best P(Seq) if O came from S1	Best P(seq)
IO	0.2016 (S2•S1)	0.2016 (S2•S1)
OO	0.096 (S1•S1)	0.096 (S1•S1)
OI	0.108 (S1•S2)	0.108 (S1•S2)

Baum-Welch example

estimating initial probabilities:

1. assume all sequences start with hidden state S1, calculate best probability
2. assume all sequences start with hidden state S2, calculate best probability
3. normalize to 1

Baum-Welch example

Now we have generated updated transition, emission, and initial probabilities. Repeat this method until those probabilities converge.

If you have guessed the wrong number of hidden states, it will be clear, though it's a very bad strategy to go through a huge range of possible hidden states to find the best model – you will over-optimize.

Applications of HMMs

- Exon finding through orthology (Haussler)
- ECG signal analysis (beat segmentation and classification)
- Analysis of microarray data especially tiling arrays
- Sequence feature prediction using homology information
- Sequence alignments, pairwise and multiple
- Analyzing ChIP-chip on tiling arrays

Finding genes

- The first gene finders were for prokaryotes
  - No introns
  - Distinct and known signals
- GLIMMER (1998, Salzberg et al.) was an early gene-finding program and was very successful
  - Only for prokaryotes (first version)
  - Tested on relatively short sequences

GENSCAN (1997)

- GENSCAN (Burge and Karlin) was a huge breakthrough in eukaryotic gene-finding, and is still used by some groups
- How is it different?
  - Assumes that the input sequence can have no genes, one gene, multiple genes, or parts of genes
  - Models all known aspects of a eukaryotic gene
  - Uses general 3-periodic inhomogeneous fifth-order Markov model of coding regions
  - Does not use specific models of protein structure or database homology

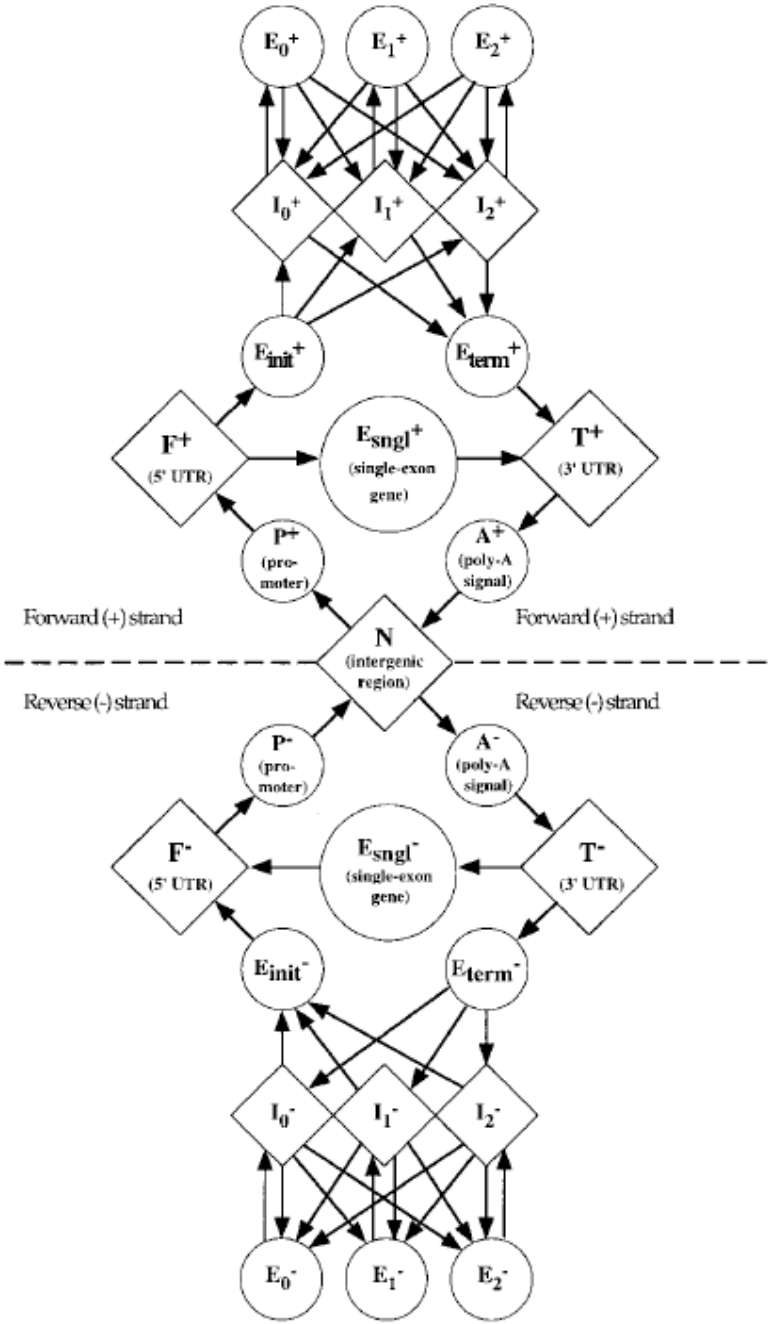
GENSCAN

- Uses double-stranded genomic sequence
- Partial genes, single gene, no genes all modeled
- Maximal Dependence Decomposition: models functional signals in DNA or protein to allow for statistical dependencies between signal positions
  - e.g. splice sites

```
exon....|GT..intron..AG|...exon
```

GENSCAN

- Explicit state duration HMM
  - Uses forward-backward algorithm
  - Choose initial state depending on the distribution of all possible states


E_0^+
E_1^+
E_2^+
I_0^+
I_1^+
I_2^+
E_{init}^+
E_{term}^+
F^+
(5' UTR)
E_{sngl}^+
(single-exon gene)
T^+
(3' UTR)
P^+
(pro-moter)
A^+
(poly-A signal)
Forward (+) strand
Forward (+) strand
N
(intergenic region)
Reverse (-) strand
Reverse (-) strand
P^-
(pro-moter)
A^-
(poly-A signal)
F^-
(5' UTR)
E_{sngl}^-
(single-exon gene)
T^-
(3' UTR)
E_{init}^-
E_{term}^-
I_0^-
I_1^-
I_2^-
E_0^-
E_1^-
E_2^-

GENSCAN — MDD

- Maximal Dependence Decomposition
  - Need aligned set of several hundred signal sequences
  - Use conditional probabilities to capture the most significant dependencies between positions
  - Calculate χ^2 for each pair of positions to detect dependencies

Next generation

- Three types of de novo predictors
  - Single genome sequence (mostly HMMs)
  - Two aligned genomes
  - Multiple aligned genomes

} infer local rates & patterns of mutation

- With good programs can expect 50-70% of the genes correctly predicted, in a compact genome

Next generation

- Single-genome predictors
  - Easier to train, faster to run
  - First step in annotation
  - Use information from intrinsic sequence signals

Next generation

- Dual-genome predictors
  - Rely on functional regions being more conserved
  - SLAM (HMM) - uses joint probability for sequence alignment and gene structure to define types of alignments seen in coding vs noncoding sequence
  - More powerful approaches use HMM and dynamic programming
  - Problem: in closely related species most of the conserved sequences are noncoding

Next generation

- Multi-genome predictors
  - More genomes -> stronger evidence
  - Hard to get enough species for a good alignment (translocations, deletions, inversions etc destroy alignments)
  - Some use phylogenetic trees (phylo-HMMs)

Common modern applications

- copy number variation
- areas of enrichment (ChIP-chip, ChIP-seq etc)
- finding CpG islands

HMM for CNV

Systematic prediction and validation of breakpoints associated with copy-number variants in the human genome

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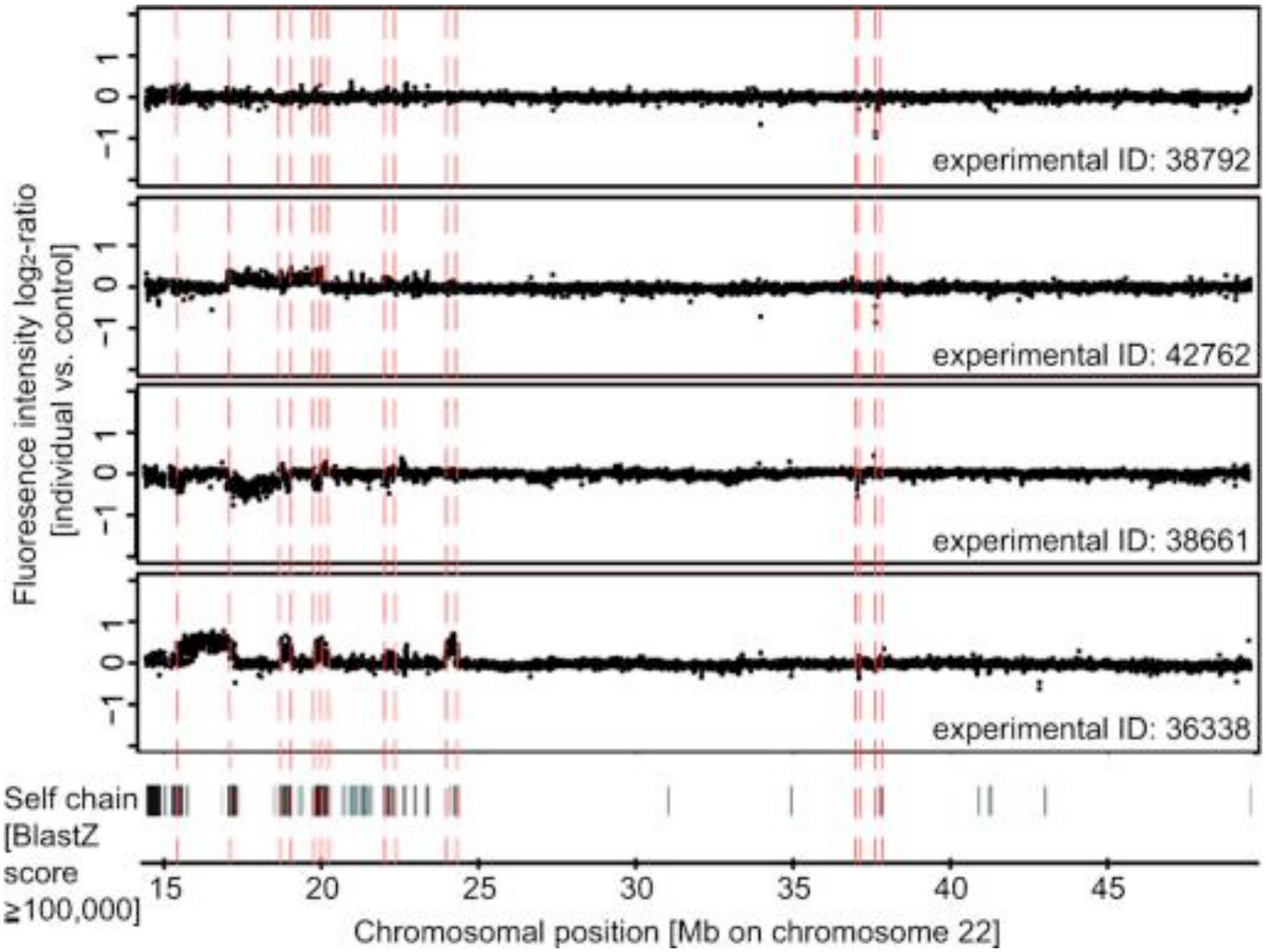
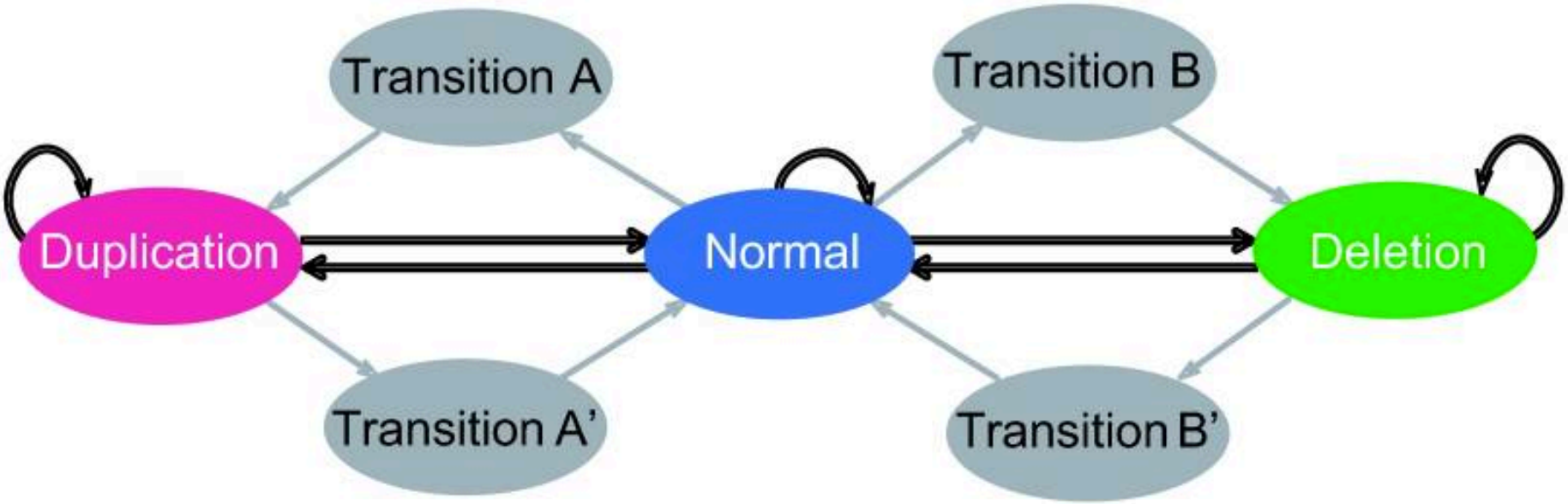
HMM for CNV


Fluoresence intensity log2-ratio
[individual vs. control]
−1 0 1
experimental ID: 38792
experimental ID: 42762
experimental ID: 38661
experimental ID: 36338
Self chain
[BlastZ
score
≥100,000]
15
20
25
30
35
40
45
Chromosomal position [Mb on chromosome 22]

HMM for CNV


Transition A
Transition B
Duplication
Normal
Deletion
Transition A'
Transition B'